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***Original Article***

# Molecular Docking and ADMET Prediction of Natural Compounds towards SARS Spike Glycoprotein-Human Angiotensin-Converting Enzyme 2 and SARS-CoV-2 Main Protease

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**Abstract**

More than a decade ago, a novel coronavirus that infects humans, bats, and certain other mammals termed severe acute respiratory syndrome coronavirus (SARS-CoV) caused an epidemic with ~ 10% case fatality, creating global panic and economic damage. Recently, another strain of the virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused an infectious disease (COVID-19) in humans which was detected for the first time in Wuhan, China. Presently, there is no specific therapy available for the treatment of COVID-19. However, social distancing, patient isolation, and supportive medical care make up the current management for this current infectious disease pandemic. The present in silico study evaluated the binding affinities of some natural products (resveratrol, xylopic acid, ellagic acid, kaempferol, and quercetin) to human angiotensin-converting enzyme 2 and coronavirus (SARS-CoV-2) main protease compared to chloroquine, an inhibitor known to prevent cellular entry and replication of the coronavirus. The respective binding energies of the selected natural compounds and chloroquine towards the proteins were computed using PyRx virtual screening tool. The pharmacodynamic and pharmacokinetic attributes of the selected compounds were predicted using admetSAR. Molecular docking analysis showed that the natural compounds had better scores towards the selected protein compared to chloroquine with polar amino acid residues present at the binding sites. The predicted ADMET properties revealed the lower acute oral toxicity of the natural products compared to chloroquine. The study provides evidence suggesting that the relatively less toxic compounds from the natural sources could be repositioned as anti-viral agents to prevent the entry and replication of SARS-CoV-2.

**Keywords:** chloroquine, COVID-19, phytochemicals, molecular docking

**Amarrage Moléculaire et Prédiction d'ADMET des Composés Naturels vers la Glycoprotéine de Pointe du SRAS-Enzyme de Conversion de l'angiotensine Humaine 2 et la Protéase Principale du SRAS-CoV-2**

**Résumé:** Il y a plus d'une décennie, un nouveau coronavirus qui infecte les humains, les chauves-souris et certains autres mammifères, appelé coronavirus du syndrome respiratoire aigu sévère (SRAS-CoV), a provoqué une épidémie avec environ 10% de fatalité, créant une panique mondiale et des dommages économiques. Récemment, une autre souche du virus, le coronavirus 2 du syndrome respiratoire aigu sévère (SRAS-CoV-2), a provoqué une maladie infectieuse (COVID-19) chez l'homme qui a été détectée pour la première fois à Wuhan, en Chine. Actuellement, il n'y a pas de thérapie spécifique disponible pour le traitement de COVID-19. Cependant, l'éloignement social, l'isolement des patients et les soins médicaux de soutienconstituent la gestion actuelle de cette pandémie actuelle de maladies infectieuses. La présente étude in silico a évalué les affinités de liaison de certains produits naturels (resvératrol, acide xylopique, acide ellagique, kaempférol et quercétine) à

l'enzyme de conversion de l'angiotensine humaine 2 et à la principale protéase du coronavirus (SARS-CoV-2) par rapport à la chloroquine, un inhibiteur connu pour empêcher l'entrée cellulaire et la réplication du coronavirus. Les énergies de liaison respectives des composés naturels sélectionnés et de la chloroquine envers les protéines ont été calculées à l'aide de l'outil de criblage virtuel PyRx. Les attributs pharmacodynamiques et pharmacocinétiques des composés sélectionnés ont été prédits à l'aide d'admetSAR. L'analyse d'amarrage moléculaire a montré que les composés naturels avaient de meilleurs scores envers la protéine sélectionnée par rapport à la chloroquine avec des résidus d'acides aminés polaires présents sur les sites de liaison. Les propriétés ADMET prédites ont révélé la toxicité orale aiguë inférieure des produits naturels par rapport à la chloroquine. L'étude fournit des preuves suggérant que les composés relativement moins toxiques provenant de sources naturelles pourraient être repositionnés en tant qu'agents antiviraux pour empêcher l'entrée et la réplication du SRAS-CoV-2.
**Mots-clés:** chloroquine, COVID-19, phytochimiques, amarrage moléculaire

## 1. Introduction

Coronavirus (CoV-2) causes severe acute respiratory syndrome (SARS), which is associated with severe shortness of breath and, sooner or later, low oxygen in the system. SARS-CoV-2, which causes a pneumonia-like illness, has spread globally ever since it was first reported in Wuhan City, China, in December 2019. The SARS-CoV-2 disease resulted in a pandemic that has so far affected over 4,800,000 people and claimed over 322,000 lives (1). The disease has also severely affected several countries including Italy, Spain, France, Germany, Iran, and the United States of America where so far, over 1,528,000 cases have been reported. Although still without a cure, several potential vaccines are reportedly currently being tested (2) while drugs for HIV, antiretrovirals, and other drugs are being repurposed as potential candidates for treatment of the disease (3).

Recently, however, the focus has shifted to chloroquine, a drug previously used in the treatment of malaria, to fight SARS-CoV-2. An *in vitro* study has shown that chloroquine possesses antiviral activities over a range of viruses (4), and recent pre-clinical testing proved the potency of the drug against the SARS-CoV-2 virus (5). It has also been shown that the chloroquine molecule acts by targeting the angiotensin-converting enzyme 2 of the SARS-CoV-2 virus (6). This process could be compared with some plant-based bioactive compounds. Phytocompounds have been evaluated and suggested as potent agents against severe acute respiratory syndrome specifically caused by coronavirus (SARS-CoV-2) activities (7). Moreover, plant products have been reported to suppress respiratory illnesses (8).

The present study aimed to investigate the intermolecular interactions of resveratrol, xylopic acid, ellagic acid, kaempferol, and quercetin with SARS Spike glycoprotein-human angiotensin-converting enzyme 2 and SARS-CoV-2 main protease and compare them with chloroquine through in silico studies.

## 2. Material and Methods

### 2.1. Molecular Docking

SARS spike glycoprotein-human angiotensin-converting enzyme 2 and SARS-CoV-2 main protease were docked separately with resveratrol, xylopic acid, ellagic acid, kaempferol, and quercetin using PyRx-Python Prescription 0.8 (The Scripps Research Institute), and the interactions were visualized using PyMOL ver. 1.1 eval (De Lano Scientific LLC, CA, USA). The 3D SDF format structures of the selected compounds were obtained from the PubChem database. The target 3D structures of SARS spike glycoprotein-human angiotensin-converting enzyme 2 (6CS2) and SARS-CoV-2 main protease (3IWM) were identified and retrieved from the Protein Data Bank (PDB). All the compounds and enzymes were converted into Auto Dock

Pdbqt format. The free energy of binding between the compounds and the proteins was computed, and the computations were compared to those generated through a similar virtual screening of chloroquine with the proteins.

### 2.2. ADMET Study

The toxicity risks of resveratrol, xylopic acid, ellagic acid, kaempferol, and quercetin were predicted based on their ADMET profiles. The ADMET (absorption, distribution, metabolism, elimination, and toxicity) studies were predicted using ADMET-SAR (http://lmmd.ecust.edu.cn/admetsar1), and the results were compared to those obtained for chloroquine. The SMILE molecular structures of the compounds were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov).

## 3. Results

### 3.1. Molecular Docking

The results of molecular docking analysis of the natural compounds as potential inhibitors of SARS spike glycoprotein-human angiotensin-converting enzyme 2 and SARS-CoV-2 main protease included their respective binding free energy (Table 1) with their corresponding interacting residues. The binding energies revealed that resveratrol, xylopic acid, ellagic acid, kaempferol, and quercetin had docking scores of −7.9, −7.8, −8.1, −7.8, and −8.0 kcal/mol, respectively, with SARS spike glycoprotein-human angiotensin-converting enzyme 2 and −6.2, −7.3, −6.6, −6.6, and −6.8 kcal/mol, respectively, with SARS-CoV-2 main protease. All the natural compounds docked showed binding energy greater than the standard drug chloroquine that presented binding energies of −6.8 and –5.4 kcal/mol with SARS spike glycoprotein-human angiotensin-converting enzyme 2 and SARS-CoV-2 main protease, respectively. The interactions between compounds and macromolecules are represented in Figures 1 and Figure 2. All the compounds interacted differently with the amino acid residues of SARS spike glycoprotein-human angiotensin-converting enzyme 2.

**Table 1.** Comparison of predicted properties of docked compounds with SARS spike glycoprotein-human angiotensin-converting enzyme 2 and SARS-CoV-2 main protease

| Compounds | PubChem CID | Properties | SARS spike glycoprotein-human angiotensin-converting enzyme 2 | SARS-CoV-2 main protease |
|---|---|---|---|---|
| Resveratrol | 445154 | Binding energy (kcal/mol) | −7.9 | −6.2 |
| | | Interacting residues | GLY-353, GLY-726, GLN-835, ASN-838, ILE-979, GLY-981 | TYR-237, ASN-238, GLY-275, MET-276, GLY-278, |
| Xylopic acid | 354614 | Binding energy (kcal/mol) | −7.8 | −7.3 |
| | | Interacting residues | PHE-558, TYR-723, VAL 956, SER-957 | MET-276, GLY-275, GLY-278 |
| Ellagic acid | 5281855 | Binding energy (kcal/mol) | −8.1 | −6.6 |
| | | Interacting residues | CYS-720, GLY-726, ARG-982 | TYR-237, ASN-238, GLY-275, MET-276, GLY-278 |
| Kaempferol | 5280863 | Binding energy (kcal/mol) | −7.8 | −6.6 |
| | | Interacting residues | TYR-725, GLY-726, PHE-837, ASP-976, THR-980, ARG-982, | TYR-237, ASN-238, GLY-275, MET-276, GLY-278, GLY-276 |
| Quercetin | 5280343 | Binding energy (kcal/mol) | −8.0 | −6.8 |
| | | Interacting residues | PHE-558, TYR-723, VAL 956, SER-957 | TYR-237, ASN-238, GLY-275, MET-276, GLY-278 |
| Chloroquine | 2719 | Binding energy (kcal/mol) | −6.8 | −5.4 |
| | | Interacting residues | CYS-720, CYS-731, ALA-732, PHE-952, ARG-977, ILE-979, GLY-981 | MET-276, GLY-275 |

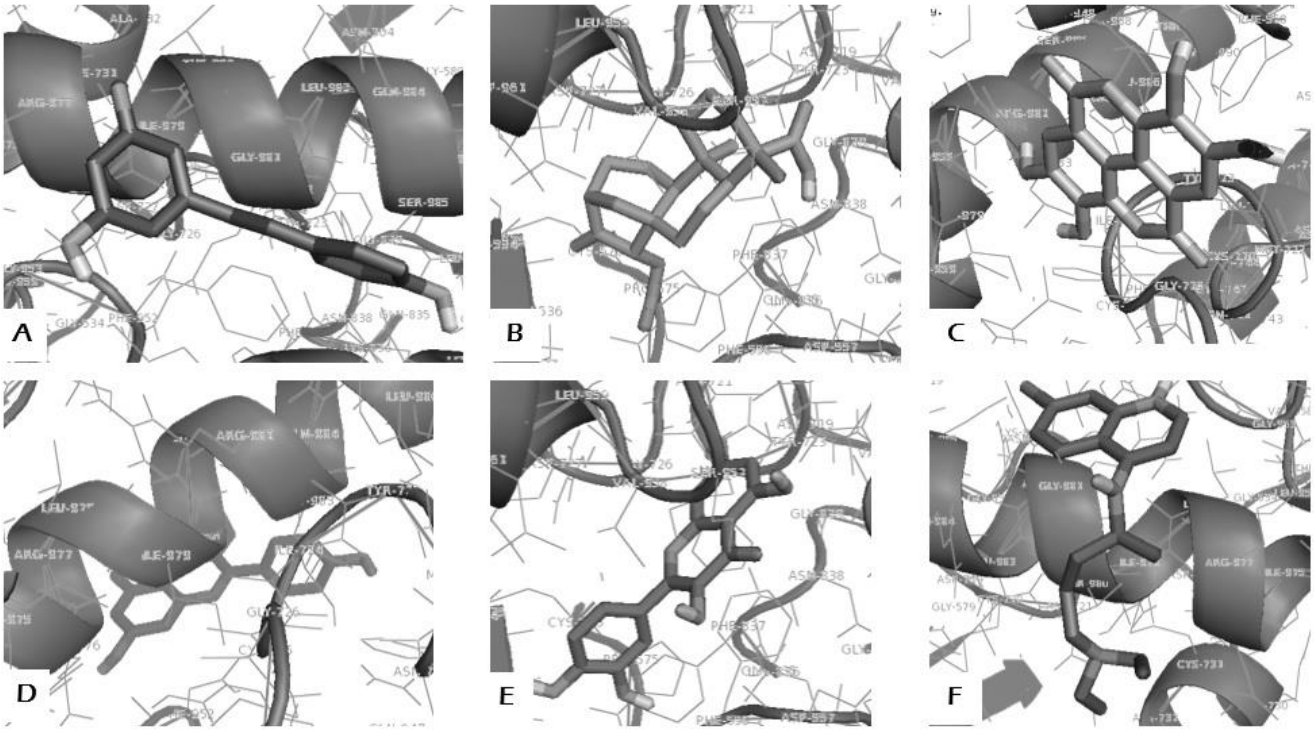


**Figure 1.** Molecular docking representation of SARS spike glycoprotein-human angiotensin-converting enzyme 2 docked with **(A)** resveratrol, **(B)** xylopic acid, **(C)** ellagic acid, **(D)** kaempferol, **(E)** quercetin, and **(F)** chloroquine

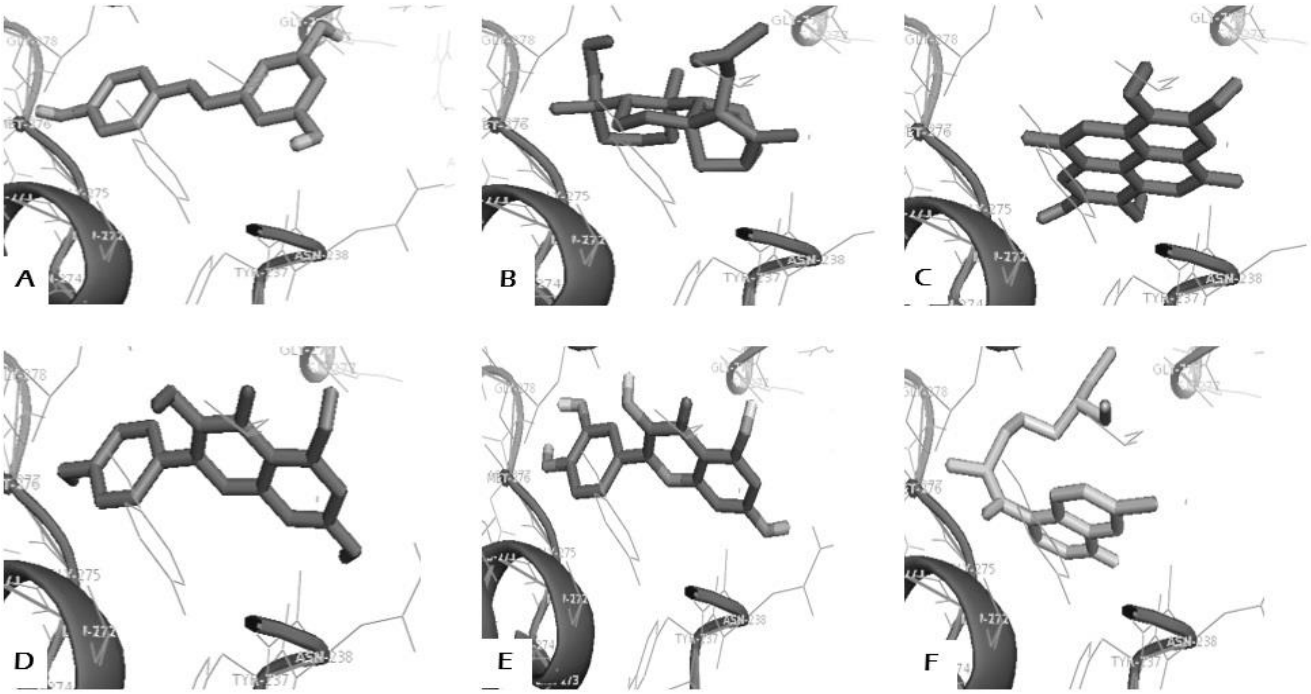


**Figure 2.** Molecular docking representation of SARS-coV-2 main protease (3iwm) docked with **(A)** resveratrol, **(B)** xylopic acid, **(C)** ellagic acid, **(D)** kaempferol, **(E)** quercetin, and **(F)** chloroquine

## 4. Discussion

### 4.1. Molecular Docking

The mechanism of action of some natural products such as resveratrol, sesamol, stilbenoids, and decitabine has been comprehensively studied. It was suggested as viral replication inhibition and synthesis of essential macromolecules such as proteins and their monomers (9, 10). Molecular docking is an important and effective structure-based in silico method that predicts interactions that would occur between a potential ligand and the biological target using a scoring function (11). In recent times, the simulation technique has been used as a hit identification and optimization tool in drug programs, fact-based drug target identification, and to determine the potential of drug repositioning (12, 13). Ellagic acid was found to have the best docking score towards SARS spike glycoprotein-human angiotensin-converting enzyme 2 followed by quercetin, resveratrol, xylopic acid and kaempferol. Moreover, xylopic acid showed the highest binding energy towards SARS-CoV-2 main protease followed by quercetin (Table 1). These high binding scores could be due to these interacting residues of the target proteins and conventional hydrogen interactions between the compounds and SARS spike glycoprotein-human angiotensin-converting enzyme 2. These selected compounds are examples of naturally occurring therapeutic agents *with poly-functional* properties found mostly in spices and other plant products which are commonly used for the treatment and management of multifactorial diseases (8, 14).

The binding of the S1 domain of the SARS-CoV-2 spike protein to angiotensin-converting enzyme 2, a metallopeptidase, and the consequent proteolytic priming of the spike protein by cellular proteases are key events in the cellular entry of SARS-CoV-2 (15). Viral proteases are vital to virus replication, and SARS-CoV-2 main protease is the enzyme that processes the proteolytic priming of SARS-CoV-2 polyproteins to the functional non-structure proteins required for viral replication and transcription (16). These proteins have been suggested as potential therapeutic targets to block cellular entry and viral replication of coronaviruses; they also enhance the development of anti-SARS drugs (17). The molecular structures showed that the compounds and their interactions with the various amino acids of the macromolecules could substantiate the observed differences in the binding affinities of the compounds (Figure 1). The presence of MET-276 in the binding pocket of SARS-CoV-2 main protease, where all the compounds interacted, suggests that any of the compounds could modulate the DNA methylation of SARS-CoV-2 main protease genes, thus limiting the replicating potential of the virus possibly through transcription repression (18-20). Furthermore, the interaction of all the compounds except chloroquine with polar amino acid residues (TYR-237 and ASN-238) of SARS-CoV-2 main protease (Figure 2) could suggest the formation of a hydrogen bond between the protein binding pockets and the ligands. This hydrogen bond could be responsible for the higher binding affinity exhibited by the ligands compared to chloroquine (21). This binding could modulate the binding of the SARS-CoV-2 main protease with its expected substrate in the host cell (22).

Additionally, there is the presence of polar positively charged residues at the binding sites of SARS spike glycoprotein-human angiotensin-converting enzyme 2 for all selected compounds except xylopic acid and quercetin. The identification of these positively charged residues could suggest that the compounds were able to bind to the angiotensin-converting enzyme, limiting its affinity for the SARS spike glycoprotein. However, the presence of no charge polar residue at the binding site of xylopic acid and quercetin with high binding affinity could probably be due to coordination between the PHE, TYR, VAL, and SER present in the active pocket of the protein. Thus, the functional properties of these interactions through simultaneous inhibition of the SARS spike glycoprotein-human angiotensin-converting enzyme 2 and SARS-CoV-2 main protease by these selected *ubiquitous phytocompounds* could markedly limit the ability of SARS-CoV-2 to proliferate in the host

in addition to their associated minimal side effects and extensive availability in plant product.

### 4.2. ADMET Study

The result of the ADMET study showed that all the compounds could cross the blood-brain barrier, were absorbed easily in the intestine, and were permeable to Caco-2. However, none of the compounds serves as a P-glycoprotein (P-gp) substrate except xylopic acid, suggesting better oral availability of the compounds and no inhibition or induction effect on metabolizing enzymes (23). Similarly, all compounds except xylopic acid showed inhibitory potential on CYP2C9 and CYP2C19, suggesting a drug-drug interaction (24) and could not hinder the metabolism of therapeutic drugs with anti-malaria, anti-ulcer, and anti-convulsant drugs as well as others (25). Remarkably, none of the compounds inhibited CYP2D6, suggesting that none of the compounds could stop the metabolism of anti-hypersensitive and anti-arrhythmic drugs and serve as β-blockers and anti-depressants. All the compounds revealed weak inhibition potential of the human ether-a-go-go-related gene (*hERG)*, whose expression plays a significant role in the repolarization of cardiac action potential (26). The salmonella typhimurium reverse mutation assay showed that all the compounds except chloroquine could induce mutation in salmonella typhimurium. The toxicities of the natural products in fish, Tetrahymena pyriformis, and bee were high. The acute oral toxicity showed that resveratrol, xylopic acid, ellagic acid, kaempferol, and quercetin were relatively safe compared to chloroquine. Moreover, the study showed that all the investigated compounds are non-carcinogenic chemicals, suggesting that they are relatively safe.

## 5. Conclusion

The results for resveratrol, xylopic acid, ellagic acid, kaempferol, and quercetin showed greater binding affinities for the SARS spike glycoprotein-human angiotensin-converting enzyme 2 and SARS-CoV-2 main protease than chloroquine, which suggests better prevention of the cellular entry and proliferation of SARS-CoV-2. Moreover, the obtained predictions of ADMET properties of the studied compounds showed that they are relatively less toxic than chloroquine. These natural products could be repositioned as antiviral natural products for experimental studies based on their predicted potencies when compared to chloroquine.

### Authors' Contribution

Study concept and design: O. I. F., O. B. J. and O. S. O.
Acquisition of data: O. I. F., O. B. J. and O. S. O.
Analysis and interpretation of data: O. I. F. and O. B. J.
Drafting of the manuscript: O. I. F., O. B. J. and O. S. O.
Critical revision of the manuscript for important intellectual content: O. I. F., O. B. J. and O. S. O.
Statistical analysis: None
Administrative, technical, and material support: O. I. F., O. B. J. and O. S. O.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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